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MM2-thalamic Creutzfeldt-Jakob disease-Neuropathological, biochemical and transmission studies identify a distinctive prion strain

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Introduction

In Creutzfeldt-Jakob disease (CJD), molecular typing based on the size of the protease resistant core of the disease-associated prion protein (PrP^{Sc}) and the M/V polymorphism at codon 129 of the PRNP gene correlates with the clinico-pathologic subtypes. Approximately 95% of the sporadic 129MM CJD patients are characterized by cerebral deposition of type 1 PrP^{Sc} and correspond to the classic clinical CJD phenotype. The rare 129MM CJD patients with type 2 PrP^{Sc} (MM2) are further subdivided in a cortical and a thalamic form, also indicated as sporadic Fatal Insomnia (sFI). To define the diversity between the MM2 subtypes, we characterized two different cases of MM2-thalamic CJD in terms of clinical, neuropathological, biochemical and transmission properties.

Material and Methods

Two young patients, both MM at codon 129 and affected by a thalamic form of CJD, were followed up to describe the clinical course and, after autopsy, the neuropathological and biochemical features were characterized. To evaluate the transmission properties, a group of gene targeted transgenic mice expressing human PrP on a mouse PrP knock-out background and carrying the MM 129 codon genotype (HuMM) were injected by a combination of intracerebral (i.c.) (20 µl) and intraperitoneal (i.p.) (100 µl) routes with 10% homogenate of cerebral cortex from one of the two MM2-thalamic cases.

Results

Main neuropathological features in the two cases were diffuse, synaptic PrP immunoreactivity in the cerebral cortex and severe neuronal loss and gliosis in the thalamus and olivary nucleus. Western blot analysis showed the presence of type 2A PrP^{Sc}. Challenge of transgenic mice expressing 129MM human PrP showed that MM2-thalamic sCJD transmitted the disease to 13 out of 14 mice, with an incubation time of 535 ± 32 (mean \pm s.e.m) days and a survival period of 557 ± 23 (mean \pm s.e.m) days. All affected mice showed mild spongiform changes in the brain and the presence of a type 2A PrP^{Sc}. Conversely, no clinical signs, neuropathological changes and PrP^{Sc} accumulation were observed in mice (n = 16) injected with a MM2-cortical case, up to 650 days post-inoculation.

Conclusions

Our data indicate that the MM2-thalamic form of CJD shows peculiar clinical, neuropathological and biochemical characteristics, and is capable to transmit the disease to mice expressing the human 129MM PRNP, at variance with MM2-cortical sCJD. The affected mice showed deposition of type 2A PrPSc, a scenario that is unprecedented in this mouse line. These data indicate that MM2-thalamic sCJD is caused by a prion strain distinct from the other sCJD subtypes including the MM2-cortical form.